

## SEARCH REQUEST FORM

Requestor's Name: \_\_\_\_\_ Serial Number: \_\_\_\_\_  
Date: \_\_\_\_\_ Phone: \_\_\_\_\_ Art Unit: \_\_\_\_\_

### Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

### STAFF USE ONLY

Date completed: 10-15-03

Searcher: Reveling - 4999

Terminal time: \_\_\_\_\_

Elapsed time: \_\_\_\_\_

CPU time: \_\_\_\_\_

Total time: \_\_\_\_\_

Number of Searches: \_\_\_\_\_

Number of Databases: 3

#### Search Site

\_\_\_\_\_ STIC

\_\_\_\_\_ CM-1

\_\_\_\_\_ Pre-S

#### Type of Search

\_\_\_\_\_ N.A. Sequence

\_\_\_\_\_ A.A. Sequence

\_\_\_\_\_ Structure

\_\_\_\_\_ Bibliographic

#### Vendors

\_\_\_\_\_ IG

☒ STN

☒ Dialog

\_\_\_\_\_ APS

\_\_\_\_\_ Geninfo

\_\_\_\_\_ SDC

\_\_\_\_\_ DARC/Questel

☒ Other CE

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ACCESS DB # \_\_\_\_\_

105566

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Location (Bldg/Room#): CM1-7E15

Mail box CHI-7E12

Scientific and Technical Information Center

# SEARCH REQUEST FORM

Date: 08 08-03 Requester's Full Name: \_\_\_\_\_ Examiner #: S. DEVI

Ext Unit: 1645 Phone (308) 9347 Serial Number: 10/030,390

Results Format Preferred (circle): PAPER DISK E-MAIL

\*\*\*\*\*

ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): WOLFGANG CHRISTIAN HANS; LOTHAR STIEDLER  
ERIK RENE REMAUT

Earliest Priority Date: 7-5-99

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the related species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known.

\*For Sequence Searches Only\* Please include all pertinent information (parent, grandchild, divisional, or issued patent numbers) along with appropriate serial number.

Please ask MS. BEVERLY SHEARS to perform this search.

Please see attached claims with key words highlighted and/or Examples and synonyms provided.

Please include the following databases: Embase, Medline, Biosis, CA (Dialog 50), JAPIO, JICTEplus, Dialog 35, 65, 77, 144, 256, 266, 440, 348, 357, 113, 129, 130, 156 and 60.

Please perform an inventor's name search.

Thank you. ☺

Please return the attached claims and this search request form along with the search reports.

## FOR OFFICIAL USE ONLY

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# Searcher Picked Up: \_\_\_\_\_

# Completed: \_\_\_\_\_

Requester Prep & Review Time: \_\_\_\_\_

File Time: \_\_\_\_\_

## Type of Search

\_\_\_\_\_ NA Sequence (#)

\_\_\_\_\_ AA Sequence (#)

\_\_\_\_\_ Structure (#)

\_\_\_\_\_ Bibliography

\_\_\_\_\_ Litigation

\_\_\_\_\_ Fulltext

\_\_\_\_\_ Other

## Vendors and Cost

\_\_\_\_\_ STN \_\_\_\_\_ Dialog

\_\_\_\_\_ Questel/Orbit \_\_\_\_\_ Dr. Link

\_\_\_\_\_ Lexis/Nexis \_\_\_\_\_ Westlaw

\_\_\_\_\_ WWW/Internet

\_\_\_\_\_ In-house sequence systems (list)

\_\_\_\_\_ Other (specify)



# **STIC Search Report**

## **Biotech-Chem Library**

**STIC Database Tracking Number: 105566**

**To: Sarvamangala Devi**

**Location: cm1/7e12**

**Art Unit: 1645**

**Wednesday, October 15, 2003**

**Case Serial Number: 10030390**

**From: Beverly Shears**

**Location: Biotech-Chem Library**

**CM1-1E05**

**Phone: 308-4994**

**beverly.shears@uspto.gov**

### **Search Notes**

10/030390

09oct03 13:30:03 User219783 Session D1969.2

SYSTEM:OS - DIALOG OneSearch

File 35:Dissertation Abs Online 1861-2003/Sep

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File 65:Inside Conferences 1993-2003/Oct W1

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File 144:Pascal 1973-2003/Sep W4

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File 266:FEDRIP 2003/Aug

Comp & dist by NTIS, Intl Copyright All Rights Res

File 440:Current Contents Search(R) 1990-2003/Oct 08

(c) 2003 Inst for Sci Info

File 348:EUROPEAN PATENTS 1978-2003/Sep W04

(c) 2003 European Patent Office

File 357:Derwent Biotech Res. 1982-2003/Oct W3

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\*File 357: File is now current. See HELP NEWS 357.

Alert feature enhanced for multiple files, etc. See HELP ALERT.

File 113:European R&D Database 1997

(c)1997 Reed-Elsevier(UK)Ltd All rts reserv

\*File 113: This file is closed (no updates)

Set Items Description

Set	Items	Description
S1	1039	((GASTROINTESTIN? OR GASTRO(W)INTESTIN? OR GASTRIC OR INTE-STIN?)(5N)(DISEAS? OR DISORDER? ?) OR CROHN? OR REGIONALIS OR COLITIS OR ULCER? OR ENTERITIS OR ILEITIS OR ILEOCOLITIS OR R-ECTOCOLITIS OR PROCTOCOLITIS) AND (LACTOBACILL? OR LA...
S2	2	S1 AND ((OESTROGEN OR ESTROGEN)(1W)PEPTIDE? ? OR TREFOIL OR TFF? ? OR PS2 OR PS(1W)2)
S3	2	RD (unique items)

>>>No matching display code(s) found in file(s): 65, 113

-Key terms

3/3,AB/1 (Item 1 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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01373563

SPRAY-DRIED MICROBIAL CELLS

SPRUH-GETROCKNETE, MIKROBIELLE ZELLEN

CELLULES MICROBIENNES SECHEES PAR PULVERISATION

PATENT ASSIGNEE:

Biofermin Pharmaceutical Co., Ltd., (3929470), 5, Sanbancho 5-chome,  
Nagata-ku, Kobe-shi, Hyogo 653-0011, (JP), (Applicant designated  
States: all)

INVENTOR:

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Hirayama, Kouichi c/o Biofermin Pharma. Co., Ltd., Kobe Fac. 3-4-7  
Ibukidai Higashimachi Nishi-ku, Kobe-shi Hyogo 651-2242, (JP)

LEGAL REPRESENTATIVE:

Teipel, Stephan, Dr. et al (86861), Lederer & Keller Patentanwalte  
Prinzregentenstrasse 16, 80538 Munchen, (DE)

PATENT (CC, No, Kind, Date): EP 1281752 A1 030205 (Basic)

10/030390

WO 2001083704 011108  
APPLICATION (CC, No, Date): EP 2001926079 010427; WO 2001JP3754 010427  
PRIORITY (CC, No, Date): JP 2000133307 000502; JP 2000339267 001107  
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI;  
LU; MC; NL; PT; SE; TR  
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI  
INTERNATIONAL PATENT CLASS: C12N-001/00; A23L-001/28; A61K-035/66;  
F26B-017/10

ABSTRACT EP 1281752 A1

An object of the present invention is to provide a method for drying the liquid of microorganism cells where, in a manufacturing step of a dried microorganism cell product or of a composition such as pharmaceutical or food containing the same, extinction or damage of microorganism cells is suppressed as much as possible and survival rate is able to be highly retained and another object is to provide a dried microorganism cell product in a single micron size having many cell numbers per unit weight and being easily made into pharmaceutical or food.

The present invention relates to a method for the manufacture of a dried microorganism cell product, characterized in that, sprayed liquid droplets in a single micron size are dried with drying wind and also to a dried microorganism cell product in a single micron size.

ABSTRACT WORD COUNT: 139

NOTE:

Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; Japanese  
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200306	461
SPEC A	(English)	200306	11626
Total word count - document A			12087
Total word count - document B			0
Total word count - documents A + B			12087

3/3,AB/2 (Item 1 from file: 357)  
DIALOG(R)File 357:Derwent Biotech Res.  
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0266187 DBR Accession No.: 2001-05941 PATENT  
Recombinant **Lactococcus** lactic for delivering a **trefoil** peptide  
useful for treating acute or chronic **gastrointestinal**  
inflammatory **diseases** or **disorders**, e.g. acute or  
**ulcerative colitis**, acute flareups of **Crohn's** disease  
- recombinant **Lactococcus lactis** useful for treating disease  
AUTHOR: Hans W C; Steidler L; Remaut E R  
CORPORATE SOURCE: Zwijnaarde, Belgium.  
PATENT ASSIGNEE: Vlaams-Interuniv.Inst.Biotechnol. 2001  
PATENT NUMBER: WO 200102570 PATENT DATE: 20010111 WPI ACCESSION NO.:  
2001-138142 (2014)  
PRIORITY APPLIC. NO.: EP 99870143 APPLIC. DATE: 19990705  
NATIONAL APPLIC. NO.: WO 2000EP6343 APPLIC. DATE: 20000705  
LANGUAGE: English  
ABSTRACT: A recombinant **Lactococcus lactis** capable of  
delivering a **trefoil** peptide in vivo, is claimed. Also claimed  
are: a method for the delivery of **trefoil** peptide to the

gastrointestinal tract; methods of treating **gastric** or **intestinal disease** or **disorders**, or lesions caused by these disorders; a method for producing a microorganism able to deliver **trefoil** peptide by transforming a microorganism with a recombinant vector carrying a **trefoil** peptide coding sequence under the control of promoter and a secretion signal sequence; and a recombinant vector containing a **trefoil** peptide coding sequence under the control of a promoter sequence and a secretion signal sequence. The recombinant microorganism is useful for manufacturing an agent for the delivery of a **trefoil** peptide to the gastrointestinal tract, and for treating **gastric** or **intestinal diseases**, or lesions caused by **gastric** or **intestinal diseases** or **disorders**. The microorganism may be used for preparing medicament to be used for treating disease, etc. Disease states which can be treated by composition containing the recombinant microorganism or **trefoil** peptides, include disorders of and damage to alimentary canal. (59pp)

- Author(s)

Set	Items	Description
S4	74	AU=(HANS, W? OR HANS W?)
S5	72	AU=(STEIDLER, L? OR STEIDLER L? OR STIEDLER, L? OR STIEDLER L?)
S6	120	AU=(REMAUT, E? OR REMAUT E?)
S7	6	S4 AND S5 AND S6
S8	7	S4 AND (S5 OR S6)
S9	55	S5 AND S6
S10	13	(S9 OR S4 OR S5 OR S6) AND S1
S11	13	(S7 OR S8 OR S10) NOT S2
S12	8	RD (unique items)

>>>No matching display code(s) found in file(s): 65, 113

12/3,AB/1 (Item 1 from file: 144)  
 DIALOG(R)File 144:Pascal  
 (c) 2003 INIST/CNRS. All rts. reserv.

15049702 PASCAL Number: 01-0207468  
 Turbo probiotics for IBD  
**STEIDLER L; HANS W; SCHOTTE L; NEIRYNCK S; OBERMEIER F; FALK W; FIERIS W; REMAUT E**  
 Departments of Molecular Biology, Ghent, University and Flanders Interuniversity of Biotechnology, Germany; Department of Medicine, University of Regensburg, Germany  
 Journal: Gastroenterology : (New York, NY. 1943), 2001, 120 (5) 1297-1298  
 Language: English

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12/3,AB/2 (Item 2 from file: 144)  
 DIALOG(R)File 144:Pascal  
 (c) 2003 INIST/CNRS. All rts. reserv.

14758707 PASCAL Number: 00-0436635  
 Treatment of murine **colitis** by **Lactococcus lactis** secreting interleukin-10  
**STEIDLER L; HANS W; SCHOTTE L; NEIRYNCK S; OBERMEIER F; FALK W; FIERIS W; REMAUT E**

10/030390

Department of Molecular Biology, Ghent University and Flanders  
Interuniversity Institute for Biotechnology, K. L. Ledeganckstraat 35, 9000  
Gent, Belgium; Department of Internal Medicine I, University of Regensburg,  
Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany

Journal: Science : (Washington, D.C.), 2000, 289 (5483) 1352-1355

Language: English

The cytokine interleukin-10 (IL-10) has shown promise in clinical trials for treatment of inflammatory bowel disease (IBD). Using two mouse models, we show that the therapeutic dose of IL-10 can be reduced by localized delivery of a bacterium genetically engineered to secrete the cytokine. Intragastric administration of IL-10-secreting **Lactococcus lactis** caused a 50% reduction in colitis in mice treated with dextran sulfate sodium and prevented the onset of colitis in IL-10 SUP - SUP / SUP - mice. This approach may lead to better methods for cost-effective and long-term management of IBD in humans.

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12/3,AB/3 (Item 1 from file: 440)  
DIALOG(R)File 440:Current Contents Search(R)  
(c) 2003 Inst for Sci Info. All rts. reserv.

16507694 Document Delivery Available: 000183886000031 References: 36

TITLE: Biological containment of genetically modified **Lactococcus lactis** for intestinal delivery of human interleukin 10

AUTHOR(S): **Steidler L (REPRINT)**; Neiryneck S; Huyghebaert N; Snoeck V; Vermeire A; Goddeeris B; Cox E; Remon JP; **Remaut E**

AUTHOR(S) E-MAIL: l.steidler@ucc.ie

CORPORATE SOURCE: State Univ Ghent, Dept Mol Biomed Res, KL Ledeganckstr 35/B-9000 Ghent//Belgium/ (REPRINT); State Univ Ghent, Dept Mol Biomed Res, /B-9000 Ghent//Belgium/; State Univ Ghent, Lab Pharmaceut Technol, /B-9000 Ghent//Belgium/; State Univ Ghent, Lab Vet Immunol, /B-9820 Merelbeke//Belgium/

PUBLICATION TYPE: JOURNAL

PUBLICATION: NATURE BIOTECHNOLOGY, 2003, V21, N7 (JUL), P785-789

GENUINE ARTICLE#: 696KL

PUBLISHER: NATURE PUBLISHING GROUP, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707 USA

ISSN: 1087-0156

LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Genetically modified **Lactococcus lactis** secreting interleukin 10 provides a therapeutic approach for inflammatory bowel disease. However, the release of such genetically modified organisms through clinical use raises safety concerns. In an effort to address this problem, we replaced the thymidylate synthase gene thyA of **L. lactis** with a synthetic human IL10 gene. This thyA - hIL10(+) **L. lactis** strain produced human IL-10 (hIL-10), and when deprived of thymidine or thymine, its viability dropped by several orders of magnitude, essentially preventing its accumulation in the environment. The biological containment system and the bacterium's capacity to secrete hIL-10 were validated in vivo in pigs. Our approach is a promising one for transgene containment because, in the unlikely event that the engineered **L. lactis** strain acquired an intact thyA gene from a donor such as **L. lactis** subsp. cremoris, the transgene would be eliminated from the genome.

12/3,AB/4 (Item 2 from file: 440)

10/030390

DIALOG(R)File 440:Current Contents Search(R)  
(c) 2003 Inst for Sci Info. All rts. reserv.

14730129 Document Delivery Available: 000178192000021 References: 65  
TITLE: In situ delivery of cytokines by genetically engineered

**Lactococcus lactis**

AUTHOR(S): **Steidler L (REPRINT)**

AUTHOR(S) E-MAIL: Lothar.Steidler@DMB.RUG.ACBE

CORPORATE SOURCE: State Univ Ghent, Dept Biol Mol, KL Ledeganckstr  
35/B-9000 Ghent//Belgium/ (REPRINT); State Univ Ghent, Dept Biol Mol,  
/B-9000 Ghent//Belgium/

PUBLICATION TYPE: JOURNAL

PUBLICATION: ANTONIE VAN LEEUWENHOEK INTERNATIONAL JOURNAL OF GENERAL AND  
MOLECULAR MICROBIOLOGY, 2002, V82, N1-4 (AUG), P323-331

GENUINE ARTICLE#: 596XP

PUBLISHER: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT,  
NETHERLANDS

ISSN: 0003-6072

LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The development of novel approaches that allow for accurate targeting of therapeutics to the bowel mucosa is a priority in the research on inflammatory bowel disease. We have engineered **Lactococcus lactis** to secrete soluble, fully active, correctly processed cytokines. We have used these live, recombinant strains for the in situ delivery of mouse interleukin (mIL)-2, -6 and -10 at airway mucosa or mucosa of the colon. Strains that secrete mIL-2 or mIL-6 and produce TTFC intracellular show a higher level of anti-TTFC induction in mice following intranasal inoculation. We showed that mIL-10 producing **L. lactis** can prevent and cure enterocolitis in mice. The daily ingestion of this strain leads to the prevention of **colitis** in IL-10 -/- 129 Sv/Ev mice. The repeated addition of DSS to the drinking water of Balb/c mice leads to the induction of chronic **colitis** with a typical mean histological score of five points. Subsequent daily treatment with 108 IL-10 producing **L. lactis** reduced the inflammation to a score of approximately 1 in 40% of the treated mice, which is a status equal to that of healthy control mice. Most other animals from the treated group only showed minor patchy remnants of the inflammation. Killing of the IL-10 producing bacteria by UV irradiation immediately prior to inoculation abrogates this therapeutic effect. Therefore it can be attributed to the active in vivo delivery of IL-10. We have further documented this by demonstrating in situ de novo synthesis of IL-10 in the colon of IL-10 -/- mice.

12/3,AB/5 (Item 1 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
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01253621

DELIVERY OF TREFOIL PEPTIDES

BEREITSTELLUNG VON PEPTIDEN MIT KLEEBLATTSTRUKTUR

DISTRIBUTION DE PEPTIDES EN TREFLE

PATENT ASSIGNEE:

Vlaams Interuniversitair Instituut voor Biotechnologie, (2152562),  
Rijvisschestraat 118, 9052 Zwijnaarde, (BE), (Applicant designated  
States: all)

INVENTOR:

**HANS, Wolfgang, Christian**, Albrecht-Durer-Weg 3, D-84034 Landshut,



10/030390

(DE)

**STEIDLER, Lothar**, Bokslaarstraat 41, B-9160 Lokeren, (BE)

**REMAUT, Erik, Rene**, Bergstraat 7, B-9921 Lonendegem, (BE)

LEGAL REPRESENTATIVE:

De Clercq, Ann (87752), De Clercq, Brants & Partners cv., Edgard

Gevaertdreef 10a, 9830 Sint-Martens-Latem, (BE)

PATENT (CC, No, Kind, Date): EP 1194554 A1 020410 (Basic)

WO 200102570 010111

APPLICATION (CC, No, Date): EP 2000954434 000705; WO 2000EP6343 000705

PRIORITY (CC, No, Date): EP 99870143 990705

DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI;

LU; MC; NL; PT; SE

EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI

INTERNATIONAL PATENT CLASS: C12N-015/16; C12N-015/74; C12N-001/21;

C07K-014/575; A61K-038/22; C12N-1:21; C12R-1:225

NOTE:

No A-document published by EPO

LANGUAGE (Publication,Procedural,Application): English; English; English

12/3,AB/6 (Item 2 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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01161352

USE OF A CYTOKINE-PRODUCING *\$(LACTOCOCCUS)* STRAIN TO TREAT  
**COLITIS**

VERWENDUNG EINES ZYTOKINE-PRODUZIERENDEN **LACTOCOCCUS** STAMMES ZUR  
BEHANDLUNG VON KOLITIS

UTILISATION DE SOUCHE DE *\$(LACTOCOCCUS)* PRODUISANT DE LA CYTOKINE  
POUR TRAITER LA COLITE

PATENT ASSIGNEE:

Vlaams Interuniversitair Instituut voor Biotechnologie vzw., (2152561),  
Rijvisschestraat 120, 9052 Zwijnaarde, (BE), (Applicant designated  
States: all)

INVENTOR:

**STEIDLER, Lothar**, Bokslaarstraat 41, B-9160 Lokeren, (BE)

**REMAUT, Erik, Rene**, Bergstraat 7, B-9921 Vinderhout, (BE)

**FIERS, Walter**, Beukendreef 3, B-9070 Destelbergen, (BE)

PATENT (CC, No, Kind, Date): EP 1123314 A2 010816 (Basic)

WO 200023471 000427

APPLICATION (CC, No, Date): EP 99950738 991006; WO 99EP7800 991006

PRIORITY (CC, No, Date): EP 98203529 981020

DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI;

LU; MC; NL; PT; SE

EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI

INTERNATIONAL PATENT CLASS: C07K-014/54; C07K-014/715

NOTE:

No A-document published by EPO

LANGUAGE (Publication,Procedural,Application): English; English; English

12/3,AB/7 (Item 1 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

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0306093 DBR Accession No.: 2003-07878 PATENT

New **Lactococcus** isolated strain having a defective thymidylate

10/030390

synthase gene, useful as host strain for transformation and for the preparation of a medicament to treat inflammatory bowel diseases, particularly **Crohn's** disease - producing mutant **Lactococcus lactis** having thymidylate-synthase gene disruption useful for drug delivery

AUTHOR: **STEIDLER L**

PATENT ASSIGNEE: VLAAMS INTERUNIVERSITAIR INST BIOTECHNOG 2002

PATENT NUMBER: WO 200290551 PATENT DATE: 20021114 WPI ACCESSION NO.:

2003-111978 (200310)

PRIORITY APPLIC. NO.: EP 2001204785 APPLIC. DATE: 20011207

NATIONAL APPLIC. NO.: WO 2002EP4942 APPLIC. DATE: 20020503

LANGUAGE: English

ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated strain of **Lactococcus** sp. comprising a defective thymidylate synthase gene, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a pharmaceutical composition comprising the novel isolated strain; and (2) a transformed strain of **Lactococcus** sp., comprising a transforming plasmid that does not comprises an intact thymidylate synthase gene. BIOTECHNOLOGY - Preferred Isolated Strain: The gene is preferably inactivated by gene disruption. The **Lactococcus** sp. is preferably **Lactococcus lactis**. Preferred Transformed Strain: The transformed strain further comprises a gene encoding a prophylactic and/or therapeutic molecule, preferably interleukin-10. ACTIVITY - Antiinflammatory. No biological data is given. MECHANISM OF ACTION - Interleukin-Agonist-10; Thymidylate-Synthase-Inhibitor. USE - The strain of **Lactococcus** sp. is useful as host strain for transformation. The transformed strain of **Lactococcus** sp. is useful for the delivery of prophylactic and/or therapeutic molecules. The pharmaceutical composition is useful for the preparation of a medicament to treat inflammatory bowel diseases. (All claimed.) The inflammatory bowel disease is **Crohn's** disease. EXAMPLE - The regions flanking the sequence were cloned from **Lactococcus lactis** MG1363. The thyA replacement was performed by making suitable replacements in a plasmid borne version of the thyA target. The thyA gene was replaced by a synthetic gene encoding a protein which has the **Lactococcus lactis** Usp45 secretion leader fused to a protein of identical amino acid sequence. At the 5' end the insertion is performed in such a way that the ATG of thyA is fused to the P1-T7Usp45-hIL-10 expression unit. At the 3' end and ACTAGT SpeI restriction site was engineered immediately adjacent to the TAA stop codon of the usp45-hIL-10 sequence. This was ligated in a TCTAGA XbaI restriction site. The resulting strains are thyA deficient, a mutant not yet described for **L. lactis**, and strictly dependent upon the addition of thymidine or thymine for growth. (65 pages)

12/3,AB/8 (Item 2 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

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0256618 DBR Accession Number: 2000-11108 PATENT

Treating inflammatory bowel diseases comprises administering a composition comprising a cytokine-producing or cytokine antagonist-producing Gram-positive bacterial strain - i.e. *Bacillus subtilis*, *Streptococcus gordonii*, *Staphylococcus xylosum* or **Lactobacillus lactis**

AUTHOR: **Steidler L; Remaut E R; Fiers W**

CORPORATE SOURCE: Zwijnaarde, Belgium.

PATENT ASSIGNEE: Vlaams-Interuniv.Inst.Biotechnol. 2000

10/030390

PATENT NUMBER: WO 200023471 PATENT DATE: 20000427 WPI ACCESSION NO.:  
2000-422481 (2036)

PRIORITY APPLIC. NO.: EP 98203529 APPLIC. DATE: 19981020

NATIONAL APPLIC. NO.: WO 99EP7800 APPLIC. DATE: 19991006

LANGUAGE: English

ABSTRACT: Use of a cytokine-producing or cytokine antagonist-producing Gram-positive bacterial strain in the preparation of a medicament treat inflammatory bowel disease. The bacteria are used in the treatment of inflammatory bowel diseases, especially chronic **colitis**, **Crohn** disease or an **ulcerative colitis** (claimed). The use of non-colonizing bacteria expressing cytokines or cytokine antagonists allows the treatment to be directed to the disease site, whilst minimizing the possibility of degradation along the gastrointestinal tract. In an example, Sv/Ev interleukin-10 (IL-10)-/- mice spontaneously developed a generalized enterocolitis between 3-8 weeks of age. 129 Of these animals were treated at 3 weeks old for 6-8 weeks with a daily intragastric inoculation of IL-10 producing **Lactobacillus lactis**. The non-treated mice showed a histological score of 4.5 points whereas the treated mice showed a score of 1.5 points, indicating that the treatment successfully reduced the development of **colitis** in mice. The preferred bacteria are *Bacillus subtilis*, *Streptococcus gordonii*, *Staphylococcus xylosus* and *L. lactis*. (39pp)

? log y

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